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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/774,278
Filing Date: January 30, 2001
Appellant(s): LANZA ET AL.

Kate H Murashige
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 09, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The obviousness rejection is also directed to claim 3, which reads on perfluorooctane. This claims was not included in the anticipation rejection.

(7) Grouping of Claims

The rejection of claims 1, 3, 7-8, 13, 17-18, 21 , 25-26, 31, 35, 68-77 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,375,931	Ostensen	4-2002

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 7-8, 13, 17-18, 25-26, 31, 35, 68-72, 74, 76-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Ostensen US Patent 6,375,931.

The instant claims are directed to methods of enhancing and measuring acoustic reflectivity of a target for Ultrasound Imaging comprising measuring reflectivity prior to raining the temperature of the bound nanoparticles, raising the temperature of said nanoparticles, measuring reflectivity after said rise of temperature and determining the change in reflectivity of the nanoparticles before and after the raising of the temperature.

Examiner has interpreted the pending claims to be directed to methods of performing ultrasound imaging comprising having bound nanoparticles in a target area, measuring reflectivity of said bound nanoparticles, raising the temperature of the bound nanoparticles, measuring the reflectivity of the bound nanoparticles after said raising of the temperature, and determining the change in reflectivity.

Note that such recitations, as "enhancing and measuring acoustic reflectivity" are viewed to be inherent in any methods of ultrasound imaging that performs the instantly claimed method steps.

Examiner has also taken the position that the continuous ultrasound imaging performed by Ostensen on a specific site inherently meets the process step limitations of the instant claims for the following reasons. Therefore, Ostensen also is viewed to anticipate the instant limitation of "enhancing and measuring acoustic reflectivity."

Ostensen discloses methods of performing ultrasound imaging comprising administering a perfluorocarbon emulsion comprising such perfluorocarbons as perfluoropentane, perfluorohexane, and even perfluorooctane to a specific region of a patient (see abstract, col 8, lines 1-60). Ostensen teaches droplets that are smaller than 10 μm and thus meets the limitations of the instant nanoparticles, because the sizes of the instant nanoparticles as described in page 21, line 7-10 of the specification encompass particles as large as 10 μm. (see col 7, lines 26-45; col 9, lines 34-38; col 35-37, and claim 4 wherein various perfluorocarbon emulsion mixtures are described).

Example 5 and 10 of Ostensen describes Ostensen's process steps wherein a perfluorocarbon emulsion is administered to a mammal. Ostensen then teaches imaging of a specific site such as heart or kidney. Ostensen specifically expresses a steady rise in enhancement of the contrast images (see col 39-40). As described by Ostensen, this steady rise of resonance intensity is attributed to an increase in microbubble size which is respectively caused by an increase in temperature of at least 5 Deg C of the perfluorocarbon liquid within the microbubbles of Ostensen. Note that Ostensen states in col 35, line 10:

Analysis of the perfluorobutane gas dispersion alone showed that at 9° C. 52% of the microbubbles were of size below 9.9 μm; this proportion was reduced to 31% when the temperature had increased to 37° C. This temperature 15 change was accompanied by a corresponding increase in the proportion of microbubbles in the size range 15–80 μm, from 8% to 42%.

Therefore, given the fact that perfluorobutane, perfluoropentane, perfluorohexane, and perfluoroheptanes are liquid at room temperature, and that microparticles containing such compounds increase in size when subject to ultrasound frequency as described above, the Examiner takes the position that the continuous ultrasound imaging over a period of time of a specific site, as described by Ostensen, is essentially a measurement of the change in reflectivity of contrast microbubbles wherein the size of these microbubbles are increased subsequent to a rise of temperature, because the intensity of contrast increases with the duration of exposure to the ultrasound frequency.

Further, Ostensen discloses the use of targeted microbubbles comprising an RGD ligand that are specific for myocardium. Thus, specific bounding of such targeted microbubbles to the myocardium in example 24 is presumed. (see examples 24 and 10, 1 (az)). Therefore, such sequence of steps described in Ostensen's patent meet the steps (a)-(d) of the instant claim 1.

Finally, Ostensen teaches the use of various therapeutic agents with his contrast agents. (see col 17-18, claims 11-17, 22-27). Accordingly, Ostensen's methods either expressly or inherently anticipate the limitations of the instant claims when Ostensen performs a continuous ultrasound imaging from a sited that is exposed to a targeted microbubble.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35, 68-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostensen.

The teachings of Ostensen are described above. Ostensen teaches the use of perfluoroctane, but fails to exemplify it. Ostensen also fails to administer his emulsion system to a human.

Nevertheless, Ostensen provides adequate support for the use of any perfluorocarbon. Further, Ostensen administers his contrast agents to dogs, which are well recognized animal models for humans. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to modify Ostensen's method and employ other art equivalent perfluorocarbon liquids such as perfluoroctane, in humans because the ordinary skill in the art would have had a reasonable expectation of success in observing optimal clinical results in humans as evident in dogs.

(11) Response to Argument

A. The pending claims should stand rejected over the teachings of Ostensen because contrary to Appellant's arguments, Ostensen must not contain gas before administration; rather, it can solely contain perfluorocarbons that are liquid at the room temperature and turn into gas after they are administered in vivo.

Appellant argues that instant claims are directed to liquid nanoparicles and that Ostensen is concerned with the behavior of gas microbbubbles and makes no suggestion that a modulation of imaging capability would occur with change in temperature of liquid nanoparticles (*see* Brief at page 4). Appellant then states that Ostensen does not disclose any method at all that involves liquid nanoparicles. (*Id.*) Appellant then concludes that the instant method claims are distinguishable from the process described by Ostensen, which only work because gas bubbles are formed.

(*Id.*). In reply Examiner states that the Board of Patent Appeals and Interferences ("The Board") should maintain the rejections for the reasons set forth below.

- **The scope of the instant claims does not exclude the formulations of Ostensen.**

In order to fully appreciate the teaching of Ostensen and why it anticipates the instant claims, Examiner draws the Board's attention to the scope of the pending claims. The standard for proper interpretation of the scope of the claims during patent Examination has been well established in the ruling of *In re Zletz*, 893 F.2d 319, 321 - 22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Accordingly, patent Examiners are to "give claims their broadest reasonable interpretation in light of the supporting disclosure." *In re Zletz*, 893 F.2d 319, 321 - 22, 13 USPQ2d 1320, 1322.

Here, contrary to Appellant's arguments, the scope and breadth of the pending claims do not exclude the formation of gas throughout the instantly claimed process steps (a)-(d). There is simply no limitation excluding formation of gas once the instantly employed nanoparticle emulsion is administered to the body, while it is being circulated in the systemic circulation to reach the target site, while it has reached the target site and is being bound, and even while the particles are being exposed to the ultrasound frequencies.

Neither the specification, nor the pending claims exclude formation of gas in the instantly employed nanoparticles subsequent to their exposure to ultrasound or even subsequent to their distribution in systemic circulation after their administration. The only limitation in the instant claims that excludes the formation of gas in the emulsion is before or at the time the instantly employed emulsion is being administered to a subject.

Note that the instant claims are directed to methods of measuring the temperature rise of liquid nanoparticle at a target site when nanoparicles are administered to target in a non-gaseous emulsion. Again, all that is required by the instant claims is that they are in non-gaseous form only at their time of administration, but not during the process or when in vivo.

The instant steps (a)-(d), recites the measuring or activity of liquid nanopartilces, but they do not exclude the formation of any gas after they are administered into the body or even after they are exposed to ultrasound waves. Examiner believes that the liquid nanopartilces employed in the instant claims, can exist in combination with gas or even become entirely a gaseous bubble when they are exposed to ultrasound waves or reach a temperature of 37 deg Celsius.

Further, there is no teachings in the specification that excludes formation of gas in a manner described above, or prohibits Examiner from interpreting the claims as they have been interpreted. Thus, the instant claims are not directed to such steps where no gas is formed during the entire procedure, because all that is required by the instant claims is that they are administered in a non-gaseous emulsion and then reach the target site in a liquid nanoparticle. Therefore, Appellants' arguments that the instant metods do not employ any gas during the entire procedure are simply inaccurate.

Finally, Examiner states that a rise of temperature secondary to the exposure to ultrasound energy is inherent once the entire target site is radiated. Therefore, even though, the prior art of record may not explicitly describe exposure of the contrast particles to ultrasound energy and a measurement of reflectivity prior or after the raising

of local temperature, Examiner has taken the view that this functionality is inherent once the particles of prior art are subject to the ultrasound energy.

- **Ostensen meets all elements of the instant claims.**

Having such interpretation of the scope of the claims, Ostensen meet all limitations of the instant claims. First, Ostensen defines the meaning of the term "gas" in his patent. At col 3, lines 9-67, Ostensen state that the term "gas" used herein includes **any substance** (including mixtures) at partial, e.g. substantial or completely in gaseous (including vapor) form at the **normal human body temperature of 37 deg C.** Therefore, the term "gas" in Ostensen includes any compound that is liquid at the Room Temperature but turns into gas at normal body temperature. Considering that room temperature is about 25 deg. C. Any compound that can exist in the form of liquid between 25-37 deg. Fall within the meaning of Ostensens' gaseous compounds.

Such compounds are described by Ostensen and also claimed in the instant application. Ostensen goes on to exemplify his gases by enumerating such compounds as "perflurorpentane, perluorohexane, perfluoroheptane, perfluorooctane etc...(see col 3, lines 38-56). Such compounds are liquid at room temperature. Therefore, Ostensen use of the term "gas" clearly includes material that are liquid at room temperature, but they turn into gas at normal human body temperature of 37 deg. C.[1]

[1] At page 5-6 of the Brief, Appellant has argued that perfluorobutane is not a gas at room temperature. Examiner acquiesce to the fact that during prosecution, Examiner has incorrectly argued that perfluorobutane is a gas at room temperature and agrees with Appellant's statement about perfluorbutane. However, Examiner adds that position held is still applicable for other fluorocarbons described in Ostensen such as perfluoropentane, perfluorohexane and perfluorooctane. In fact, Examiner unintentional error is merely a minor informality caused by enumeration of various similar perfluorocarbon species at issue. Nevertheless, the rejection of record should not fall because throughout the prosecution Examiner put Appellant on full notice that other fluorocarbons such as perfluoropentane,

Examiner further clarifies that steps (a)-(d) describe features of ultrasound imaging that is already inherent to the act of ultrasound imaging. With respect to the limitations of (a) measuring reflectivity prior to raising the local temperature, (b) raising the local temperature, (c) measuring reflectivity after raising the temperature and (d) determining the change of reflectivity after a rise of temperature, Examiner states that scope of such limitations fall within the scope of the process of ultrasound imaging. Examiner specifically asserts that a rise of temperature secondary to the exposure to ultrasound energy is inherent once the entire target site is radiated. Examiner adds that the act of ultrasound imaging measures reflectivity before and after the exposure to ultrasound energy. Thus, all elemental steps of (a)-(d) already is met by local application of ultrasound energy.

Ostensen discloses methods of performing ultrasound imaging comprising administering a perfluorocarbon emulsion comprising such perfluorocarbons as perfluoropentane, perfluorohexane, and even perfluoroctane to a specific region of a patient (*see* abstract, col 8, lines 1-60). Such perfluorocarbons are the same as those instantly envisioned and claimed.

Ostensen teaches droplets that are smaller than 10 μm and thus meets the limitations of the instant nanoparticles, because the sizes of the instant nanoparticles, as described in page 21, line 7-10 of the specification, encompass particles as large as 10 μm. (*see* Ostensen at col 9, lines 34-38; col 35-37, and claim 4-5, 16-18 wherein

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perfluorohexane and perfluorooctane have been described in Ostensen which fall with scope of the instant claims and properly used in the rejection.

various perfluorocarbon emulsion mixtures are described). Thus, Ostensen meets the carrier system of the instant claims.

Appellant's also argues that Ostensen's methods deal with gas dispersion and rely on expansion of gas bubbles and that the instant claims are directed to measuring the reflectivity of nanoparticles where the nanoparticles are in liquid form. (*see* Brief at page7).

In reply Examiner states that Appellant merely misinterprets the teaching of Ostensen. First, Ostensen clearly describes that gas can include any compound that is gaseous when *in vivo*. Accordingly, the use of compounds that are liquid at room temperature but turn into gas in vivo is not a teaching away from Ostensen. (see col 3, lines 8-67).

Ostensen then allows mixtures of such compounds with diffusible components that can be in the form of volatile liquids, and precursors capable of gas generation upon administration when in vivo (see col 6, lines 6-21). Ostensen states that such diffusible components is preferable a liquid at processing and storage and include perflouropentane, hexafluorobutane, decafluoropentane, perfluorohexane, perfluorooctane, perfluorodecanes etc. (*see* col 8, line 11-20, and lines 50-67).

Ostensen even allows the use of azotropic mixtures that are in liquid form at room temperature (see col 13, lines 51-66). If fact, Ostensen exemplifies liquid emulsions containing perfluoropentane and perfluorohexanes in an azotropic mixture (*see* col 23, lines 25-col 24, line 45; col 27, lines 8-24). All such mixtures are in liquid form at room temperature even though they may become gaseous *in vivo* or at the site

when subject to ultrasound waves. Ostensen then uses such mixtures for acoustic reflection (see col 37, lines 5-col 38, line 67).

Further, even Ostensen's comparative emulsion meets the limitations of the instant claims, because they contain microparticles in liquid form prior to their administration and are then subject to ultrasound frequencies (see col 40, lines 20-27). Certainly perfluoropentane, and perflurohexanes are not a gas at room temperature or before they are applied *in vivo* (col 3, lines 50-65). They may convert to a vapor or gas when subject to ultrasound energy or a rise of local temperature at the site of interest. The instant claims do not exclude such comparative formulations of Ostensen, nor do the claims exclude formation of gas after the instant liquid nanoparticles are exposed to ultrasound energy or a rise in the local temperature. Therefore, Ostensens' compositions meet the instantly employed compositions.

In fact, Ostensen alternative mode of administration also meets the limitations of the instant claims. Ostensen teaches alternative mode of administration wherein the diffusible component is administered separately from the gas-generating component. (see col 44). Accordingly, a plain reading of such teachings shows that the gas generating emulsion such as perfluorobutane or perfluoropentane and the diffusible component such as perfluorhexane or perfluroheptane are administered separately but simultaneously via a Y-piece connector and through a catheter (see col 44, lines 4-67, also see examples 9-10). Accordingly, the diffusible component of Ostensen's emulsion was in liquid form prior to administration because it contained no gaseous component. Subsequently, Ostensen's compositions meet the limitations of the instantly employed

compositions. Therefore, the instant process steps falls within those described by Ostensen.

Finally, Examiner states that a rise of temperature secondary to the exposure to ultrasound energy is inherent once the entire target site is radiated. Therefore, even though, the prior art of record may not explicitly describe exposure of the contrast particles to ultrasound energy and a measurement of reflectivity prior or after the raising of local temperature, Examiner has taken the view that this functionality is inherent once the particles of prior art are subject to the ultrasound energy. (*see* the Final Rejection at page 8).

Ostensen teaches imaging of a specific site such as heart or kidney. Ostensen specifically expresses a steady rise in enhancement of the contrast images (see col 39-40). As described by Ostensen, this steady rise of resonance intensity is attributed to an increase in microbubble size, which can only be caused, by an increase in temperature of the perfluorocarbon within the micorbubbles of Ostensen. Therefore, ultrasound measurements of reflectivity of micobubble are in fact a reflectivity measurement of the local microbubbles prior and after their exposure to the ultrasound waves.

See for example, col 31-34 wherein all in vitro characterization of microbubbles growth was accomplished by a 20 deg rise of temperature of the perfluorocarbon emulsion. Therefore, the teaching's of Ostensen is at least implicit as to the conversion of a portion of perfluorocarbon gaseous precursors or emulsion to gas upon the rise of temperature subsequent to the exposure to ultrasound waves. It goes without saying that Ostensen shows a steady rise of the size of the microbubbles. Thus, at any degree

rise of temperature, more gaseous precursors are converted to gas to intensify the expansion of the microbubbles in vivo. Applicant has not yet provided any evidence to show the contrary.

B. The pending claims should stand rejected by the teachings of Ostensen because contrary to Appellant's arguments Ostensen teaches the rise of temperature subsequent to the administration of ultrasound frequencies.

As the initial matter, the Obviousness rejection of record is only directed to Ostensen's mere failure to use or exemplify the use of perfluorooctane in his methodologies. Accordingly, for the reasons of record Examiner has maintained his position that using perfluorooctane in Ostensen's methods was obvious because Ostensen himself encourages the use of perfluorooctane in his formulations. Since Appellant has not addressed or challenged this line of reasoning, the Board should find Examiner's reasoning sufficient to affirm the obviousness rejection

Nevertheless, Appellant has challenged the rejection on the basis that it lacks the explicit teaching of a limitation that has already been discussed under the anticipation rejection. Appellant argues that Ostensen lack the explicit teaching about the rise of temperature during the ultrasound imaging process. Appellant states that Ostensen's teachings do not show that any temperature change is associated with the imaging process. (*see* Brief at page 7). In fact appellant states that Ostensen describes "no mention of temperature rise." (*Id.*). Accordingly, Appellant concludes that the present invention observes a change in reflectivity due to change in temperature in the context of an entirely liquid system. (*Id.*)

In response Examiner states that as argued above in paragraph 11, section A, of this Answer, a rise of temperature secondary to the exposure to ultrasound energy is inherent once the entire target site is radiated. Even though, the Ostensen may not explicitly describe exposure of the contrast particles to ultrasound energy to measure the reflectivity prior or after the raising of local temperature, Examiner has taken the view that this functionality is inherent once the particles of prior art are subject to the ultrasound energy.

For clarification, Examiner states that Ostensen teaches imaging of a specific site such as heart or kidney. Ostensen specifically expresses a steady rise in enhancement of the contrast images due to improved microbubble resonance (see col 39-40). As described by Ostensen, this steady rise of resonance intensity is attributed to an increase in microbubble size, which can only be caused by an increase in temperature of the perfluorocarbon within the micorbubbles of Ostensen and subsequent expansion of the microbubble. Therefore, ultrasound measurements of reflectivity of micobubble are in fact a reflectivity measurement of the local microbubbles prior to expansion and after their expansion, which is subsequent to their exposure to the ultrasound waves leading to a local temperature rise.

Examiner draws the Board's attention to col 30-34 of Ostensen to support such reasoning. According to the teachings articulated in col 30-34 of Ostensen, all *in vitro* characterization of microbubbles growth, was accomplished by at least a 20 deg Celsius rise of temperature of the perfluorocarbon emulsion. Therefore, the teaching's of Ostensen is at least implicit as to the conversion of a portion of perfluorocarbon

gaseous precursors *in vivo* upon a rise of local temperature subsequent to the exposure to ultrasound waves.

It goes without saying that Ostensen shows a steady rise of the size of the microbubbles by gradually increasing the temperature. Thus, when in vivo, at any degree rise of temperature, more gaseous precursors are converted to gas to intensify the expansion of the microbubbles leading to an improved ultrasound image. Appellant has simply provided no explanation how can the microbubbles of Ostensen containing liquid perfluorocarbon expand in size, other than, experiencing a rise in the of temperature of microbubble at the target site. Thus, the rejection should be maintained. For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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August 29, 2005

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